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COMPLETE SPECIFICATION

Improvements in the Manufacture of Complex Protein Compounds

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The present invention is concerned with a process for the production of therapeutically valuable complex protein compounds of the metal-complex salts of the chlorophyll and porphyrin series, as well as of their decomposition products, such as the bilirubinoids.

Various processes are known for the production of fibrin from fresh blood. However, complex protein-chlorophyll and -chlorophyllin products have not, however, hitherto been described.

According to the present invention there is provided a process for the production of complex protein compounds of metal complexes of the chlorophyll and porphyrin series, as well as of their decomposition products, such as bilirubinoids, wherein a solution of a proteinaceous substance is added to a solution of a metal complex of the chlorophyll or porphyrin series or of a decomposition product thereof, such as a bilirubinoid, and the resulting complex compound isolated in a known manner.

If the proteinaceous substance used contains fibrin (e.g. fresh blood), the compounds obtained are complex fibrin-metal-chlorophyll or -chlorophyllin compounds in which the chlorophyll or chlorophyllin is combined with the fibrin in such a manner that it cannot be leached out with water.

All proteinaceous substances, such as native proteins, for example blood plasma and milk albumen, are suitable for the process according to the present invention but water-soluble or water-solubilized proteins are particularly suitable.

[Price 3s. 6d.]

The products produced by the process according to the present invention may be precipitated from the reaction mixture by the addition of a suitable protein-precipitating agent, such as alcohol or acetone. However, instead of precipitating the complex products, they may also be obtained by spray-drying the reaction mixture *in vacuo*. When the products are obtained by precipitation, they are filtered off and, if necessary, dried.

The dried products can be used therapeutically in the form of fine powders but they can also be further worked up into the usual forms of medicaments.

The following Examples are given for the purpose of illustrating the invention:—

EXAMPLE 1

7.5 litres of fresh animal blood, for example sheep, pig or horse blood, are added, immediately after having been withdrawn from the animal, to 2 litres of a 0.250% solution of a chlorin e_6-copper-sodium salt.

The mixture is allowed to stand for a few hours until coagulation sets in and the separation of the fibrin-chlorin e_6-complex commences. As soon as the complex has entirely precipitated, the reaction mixture is filtered and the compound obtained washed with water until the washing water no longer contains blood-colouring matter. It is then carefully dried, if necessary *in vacuo*.

EXAMPLE 2

6 litres of fresh animal blood are introduced under the above working conditions into 2 litres of a 0.3% solution of a rhodin-g_7-copper complex sodium salt and worked up as described above.

EXAMPLE 3

Fresh blood from a slaughter house is first treated with an anti-coagulant, such as a mixture of phosphates and pyrophosphates, and the whole then centrifuged in order to remove the solid constituents; the blood plasma so obtained is used for the further working up.

1.5 gms. of chlorin e_6-copper-sodium salt

are first dissolved in a small quantity of water and then added to 2 litres of plasma with good stirring. 2 litres of acetone are then added portionwise at room temperature and with good stirring to the reaction mixture. The resulting complex protein-chlorin-e_6 compound is isolated by filtration.

The complex compound obtained is, if necessary, dried *in vacuo*. The chlorin e_6-copper component is chemically firmly bound in the complex compound obtained so that it cannot be washed out with water, alcohol or acetone.

EXAMPLE 4

100 gms. "labcasein" are converted by the addition of an alkali, such as a dilute solution of caustic soda, into a sodium-casein solution. To this solution there is added, with good stirring, an acetone solution containing 1.5 gms. of copper pheophytin. The resultant product is worked up in the above-described manner.

EXAMPLE 5

An aqueous solution containing 1.5 gms. of haematoporphyrin-Fe complex sodium salt is added to 1 litre of egg albumen. The resultant complex compound is precipitated, with good stirring, by the addition of 1 litre of ethanol.

EXAMPLE 6

2 litres of chlorin e_6-iron-sodium salt solution are introduced into two litres of plasma. The reaction mixture is then carefully sprayed *in vacuo* and the powder obtained isolated for further working up.

Chlorin e_6 and rhodin g_7 used in the above Examples are described by H. Fischer and H. Orth in "Die Chemie des Pyrrols", Vol. II, 2/1940, p.91 et seq. and in Example 14 of Patent Specification No. 407,486. "Labcasein" is a protein which has been coagulated by an enzyme, such as rennet.

The complex compounds according to the present invention are most suitable as wound medicaments. They are very effective in promoting coagulation and epithelisation of the tissues and are advantageously used in the treatment of wounds, such as flesh wounds, burns and badly healing ulcers.

WHAT WE CLAIM IS:—

1. Process for the production of complex protein compounds of metal complexes of the chlorophyll and porphyrin series, as well as of their decomposition products, such as bilirubinoids, wherein a solution of a proteinaceous substance is added to a solution of a metal complex of the chlorophyll or porphyrin series or of a decomposition product thereof, such as a bilirubinoid, and the resulting complex isolated.

2. Process according to claim 1, wherein the proteinaceous substance is animal blood, blood plasma, milk albumen or egg albumen.

3. Process according to claim 1 or 2, wherein the complex product is isolated by precipitation with a protein-precipitating agent.

4. Process according to claim 3, wherein the protein-precipitating agent is alcohol or acetone.

5. Process according to claim 1 or 2, wherein the complex product is isolated by spray drying *in vacuo*.

6. Process for the production of complex protein compounds of metal complexes of the chlorophyll and porphyrin series, as well as of their decomposition products, such as bilirubinoids, substantially as hereinbefore described with reference to any of the specific Examples.

7. Complex protein compounds of metal complexes of the chlorophyll and porphyrin series, as well as of their decomposition products, such as bilirubinoids, whenever prepared by the process according to any of claims 1—6.

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(54) SPRAY DRYING PROCESS

(71) We, BOEHRINGER MANNHEIM G.M.B.H., of Mannheim-Waldof, Germany, a Body Corporate organised under the laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention is concerned with a spray drying process for the preparation of readily water-souble friable dry powders and granulates.

For recovering labile dry substances from solutions, there can only be used drying processes which operate at low temperatures. The so-called freeze drying process admittedly ensures an optimum careful treatment of the material to be dried and thus is especially suitable for pharmaceuticals which are sensitive to hydrolysis but freeze-drying plants have the disadvantage of being very expensive not only in the provision thereof but also in operation; furthermore, the capacity of such plants is relatively low, due to the necessarily discontinuous method of operation and the comparatively high cost of apparatus.

Consequently, attempts have been made to replace freeze drying by the cheaper and simpler process of spray drying at low temperatures however, these attempts have been unsuccessful because the droplets which are formed in the spraying of very viscous or hygroscopic liquids merely inflate to form hollow spheroids with residual water in the middle which subsequently agglomerate to form lumps which can subsequently only be dissolved again with great difficulty. This undesirable effect can admittedly be countered by a drastic increase of the drying temperature but this leads to damaging of the material to be dried, even in the case of very short drying time.

In order to overcome this problem, it was suggested some years ago to add to the aqueous solutions or suspensions, before the spray drying, a low boiling solvent which was intended to explode the above-mentioned hollow spheroids during the drying process due to its high vapour pressure (see Chemiker-Zeitung, 15/16, 156/1942).

In experiments which we have carried out, we have now found that the desired effect is not obtained in the case of the drying of hygroscopic and/or viscous liquids. The hollow spheroids mentioned in the above literature reference are admittedly formed due to the evaporation of the solvent but, before the formation of a dry and thus sufficiently stable skin, they explode and those again collapse. The small amount of solvent (2—6%) has, in the meantime, evaporated so that, in the same way as in the case of spray drying without the addition of solvent, lumps are formed which considerably impair not only the further drying but also the redissolving of the dry substance. It should also be mentioned that the dried materials also subbornly retain not inconsiderable amounts of the solvent so that they cannot be used as pharmaceuticals for parenteral administration.

We have now found that the above-mentioned disadvantages can be avoided in a simple manner by the addition of ammonium salts of volatile acids to the aqueous solutions of the substance to be dried.

As ammonium salts of volatile acids, ammonium bicarbonate is preferred but there can also be used, for example, ammonium nitrite.

Not only the bulk volume but also the residual moisture in the dried product is

[Price 25p]

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dependent upon the concentration of the ammonium salts in the wet material. Since these properties are also dependent, to a large extent, upon the product the optimum concentration should be previously ascertained by experimental dryings. However, the concentration is maintain approximately within the limits of 2—5%; in the case of ammonium bicarbonate, it is about 3%.

Thus, according to the present invention, there is provided a spray drying process for the preparation of readily water-soluble, friable dry powders or granulates, wherein to an aqueous solution of a substance to be dried, before carrying out a spray drying process in the usual manner, there is added an ammonium salt of a volatile acid or of an acid which readily decomposes into volatile components, in a concentration of 2—5%, preferably about 3%, and the dried material is brought, during the drying process, to a temperature at which the added salt volatilises.

Surprisingly, with the process according to the present invention, there are obtained dry products which have optimum dissolving properties and, furthermore, are friable to a high degree. Even such extraordinarily hygroscopic medicaments as, for example, sodium chloramphenicol-succinate, are obtained with a dry quality which is not exceeded even by the considerably more expensive freeze drying process. The added materials also have the advantage that they volatilise completely, i.e. they cannot be detected in the final product, even with modern analytical methods, such as gas chromatography. Furthermore, the individual particles of the dry material are, during the drying process, surrounded by a continuously renewed, reducing, ammonia-containing atmosphere which, especially in the case of medicaments which are sensitive to oxidation, forms an additional protection against oxidative decomposition.

The dry substances prepared by the process according to the present invention dissolve again very quickly because of the large surface area due to the characteristic microstructure thereof and, because of the low drying temperatures used, they normally do not contain any decomposition products so that pharmaceuticals thus prepared are especially suitable for parenteral administration.

The process according to the present invention can be carried out continuously in the conventional apparatus used for spray drying without any changes being necessary so that a substantially more economical method of drying is now available, as compared with freeze drying. As drying plant, those have proved to be especially useful which dry the product in co-current and permit a microbe-free separation in a cyclone. The spraying can take place not only with one-substance nozzles but also with two-substance nozzles, as well as by means of spray plates. The atmospheric humidity is so adjusted according to the evaporation capacity and initial humidity that an air exit temperature of 80°C. is, if possible, not exceeded. In the case of a spray drier with a minimum evaporation capacity of 10 litres of water per hour, there is obtained, with an air throughput of 300 m³/hr., an entry temperature of 200°C., the exit temperature thereby being 70—73°C.

Since there is immediately formed a thoroughly dry and friable material, it is prevented from the very beginning that the sprayed wet material remains in the apparatus as a sticky mass or gets into the collecting device still in the form of moist and useless material. For this reason, by means of the process according to the present invention, there can also be prepared readily soluble, friable dried substances from sugar-containing syrups, for example caramel, sweetened condensed milk and malt sugar syrup. Foodstuffs and flavouring materials of low viscosity, such as coffee, cocoa or tea, also give a very readily soluble and friable dried substance which, if desired, can subsequently be granulated.

Since, during the drying procedure, neither inflammable solvent vapours nor aggressive gases are formed, it is possible to omit the provision of additional explosion and corrosion protection for the plant employed.

The following Examples are given for the purpose of illustrating the present invention:—

EXAMPLE 1

Sodium chloramphenicol-succinate.

By dissolving chloramphenicol-hemisuccinate in water and careful neutralisation with a 10% aqueous solution of sodium hydroxide, there is prepared a 50% aqueous solution of sodium chloramphenicol-succinate. When the neutralisation is completed (pH 6.9), stirring is continued for some time until the yellowish solution has become clear. To this solution is then added a 15% aqueous solution of ammonium bicarbonate in an amount sufficient to give a content of 3% of ammonium bicarbonate, referred to the dry product, and the solution is then subjected to a sterile filtration. Subsequent spray drying of the filtered solution is carried out in a spray drier with a drying capacity of 10 litres of water per hour.

Technical data:
amount of air: 300 m³ per hour
air entry temperature: 200°C.
air exit temperature: 70°C.
throughput: 5 kg. dry substance per hour.

There is obtained a dry product which contains 98.7% sodium chloramphenicol-

succinate and only 1.3% of water; the bulk density is 10 g./30 cc. Since the particle size of the product obtained is only 10—30 μm., it dissolves in water extraordinarily quickly and completely.

EXAMPLE 2

Chloramphenicol succinate arginine salt.

800 g. chloramphenicol-hemisuccinate are slowly dissolved in 1000 ml. demineralised water, while stirring. Subsequently, 326.3 g. L - (+) - arginine are introduced portionwise. The solution is further stirred for about 45 minutes until clear and, after the addition of 3% ammonium bicarbonate, referred to the solids content, is subjected to a sterile filtration. The filtered solution is spray dried in a spray drier with a capacity of 10 litres of water per hour.

Technical data:
amount of air: 300 m³ per hour
air entry temperature: 190°C.
air exit temperature: 78°C.
throughput: 5 kg. dry substance per hour.

The dry product thus obtained contains 98.5% chloramphenicol-succinate arginine salt and 0.9% water, has a bulk density of 10 g./30 cc. and under the microscope gives a characteristic picture of fragmentary or spheroidal particles with a diameter of 10—70 μm. This chloramphenicol-succinate arginine salt dissolves completely in 30 seconds in the threefold amount of water at 20°C.

EXAMPLE 3

Magnesium chloramphenicol-succinate.

84 g. magnesium hydroxide carbonate are added, with stirring, to 1.4 litres of demineralised water. Into the mixture thus obtained there are subsequently introduced portionwise 735 g. chloramphenicol-hemisuccinate. After stirring for several hours, a clear yellowish solution is obtained which, after the addition of 3% ammonium bicarbonate, referred to the solids content, and after sterile filtration, is spray dried under the conditions described in Example 2.

The dry product this obtained contains 98.5% magnesium chloramphenicol-succinate and 0.9 water and has a bulk density of 10 g./30 cc.

EXAMPLE 4

Friable caramel.

11.7 kg. of a 73% caramel solution are diluted with 5.3 kg. water so that there is obtained a 50% solution with a pH value of 4.1. While stirring intensively, 470 g. ammonium bicarbonate are gradually added portionwise, the pH thereby increasing to 7. The solution thus prepared is then spray dried.

Technical data:
entry temperature: 150°C.
exit temperature: 70°C.
amount of air. 400 m³/hour.

There is obtained a loose and readily friable powder which dissolves spontaneously in water.

EXAMPLE 5

Friable caramel.

11.7 kg. of a 73% caramel solution are diluted with 5.3 kg. water so that there is obtained a 50% solution with a pH value of 4.1. While stirring intensively, 470 g. ammonium nitrite are gradually added portionwise, the pH thereby increasing to 7. The solution thus prepared is then spray dried.

Technical data:
entry temperature: 150°C.
exit temperature: 70°C.
amount of air: 400 m³/hour.

There is obtained a loose and readily friable powder which dissolves spontaneously in water.

WHAT WE CLAIM IS:—

1. Spray drying process for the preparation of readily water-soluble, friable dry powders or granulates, wherein to the aqueous solution of a substance to be dried, before carrying out the spray drying, there is added an ammonium salt of a volatile acid or of an acid which readily decomposes into volatile components, in a concentration of 2—5% and the material to be dried is brought, during the drying process, to a temperature at which the added salt volatilises.

2. Spray drying process according to claim 1, wherein the ammonium salt is added in a concentration of 3%.

3. Spray drying process according to claim 1 or 2, wherein the ammonium salt used is ammonium bicarbonate or ammonium nitrite.

4. Spray drying process according to any of the preceding claims, whenever used for spray drying a parenterally administerable pharmaceutical.

5. Spray drying process according to claim 4, wherein the parenterally administerable pharmaceutical is a chloramphenicol-succinate salt.

6. Spray drying process according to any of claims 1—3, whenever used for spray drying a solution of a sugar or caramel.

7. Spray drying process according to any of claims 1—3, whenever used for spray drying a liquid foodstuff or flavouring.

8. Spray drying process according to claim 7, wherein the liquid foodstuff or flavouring is milk, coffee, cocoa or tea.

9. Spray drying process according to claim 1 for the preparation of readily water-soluble

and friable dry powders and granulates, substantially as hereinbefore described and exemplified.

10. Readily water-soluble and friable dry powders, whenever prepared by the process according to any of claims 1—9.

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